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Estimating Cancer Risks to a Population

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Three important issues impinge on estimating the risk of cancer to a population: (1) How can one use epidemiologic studies on one population to tell us what is likely to happen to other populations? (2) How can one use nonhuman data (i.e., laboratory experiments) to tell us what is likely to happen to humans? (3) What reasonable assumptions can be used to guide the logical extension of information from the laboratory to expectations for man, and what research is needed to support or modify these assumptions? Four principles currently guide our laboratory-to-man extrapolations: effects in animals, properly qualified, are applicable to man; methods do not now exist to establish a threshold for long-delayed effects such as cancer; the exposure of experimental animals to high doses is a necessary and valid method of discovering possible carcinogenic hazards in man; materials should be assessed in terms of human risk rather than as "safe" or "unsafe."

The risks of ingesting pollutants can be estimated with data from two sources. Data come from the laboratory and from the outside world (epidemiology). Laboratory studies range from DNA modification experiments through mutagenesis studies on cells in culture, to life-time animal-feeding studies. The animal studies usually expose relatively few animals to characterized pollutants at known concentrations. Epidemiological studies deal with human populations. They are sometimes characterized as constructing the analyses of experiments conducted by nature, involving large numbers of people. Nature shows no evidence of any formal training in experiment design, so exposure to the pollutant in question is commonly uncertain and more often than not confounded by exposures to other pollutants.

Both types of study aim to provide information on the risk to man. Laboratory studies often can provide precise information on relatively high risks related to individual pollutants in this or that animal species, before, during, or after exposure to man. Epidemiologic studies can provide less precise information on the risk to man and often require sophisticated statistics to isolate effects of one pollutant from the effects of the other pollutants which are usually present.

For materials newly introduced into the environment or to which humans are not yet exposed, the only way to assess possible risk to humans is through laboratory studies. For materials which may cause cancer, "newly introduced" means anything more recent than 25 or 30 years ago, because cancers usually do not appear until 25–30 years after people have been exposed. For materials which have been in the environment longer, epidemiologic studies are more likely to be useful. Epidemiology has discovered most of the known causes of cancer in man. With the improved ability of the laboratory to discover potentially dangerous material—and more and more materials entering the environment—imaginative crosslinking between laboratory and epidemiologic data has become of the utmost importance.

Pollutants have many different effects. At one extreme, they cause cloudless skies to be grey, our eyes to smart, our noses to run, and the civil authorities to issue air pollution "alerts," about which the community seems to not know what to do. While people puzzle about action, the wind changes, it rains, the skies clear, and we wait for the next incident. At the other extreme, the human health effects of a carcinogen present in the air are likely to go undetected, particularly if the carcinogen produces only a modest increase in the incidence of a common cancer, and if that increase occurs only many years later.

Acute effects are usually quickly perceived and can often be dealt with in the short term. However, identification and characterization of pollutants that lead to chronic, irreversible, progressive diseases such as cancer is much more difficult. In addition to

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characterizing pollution we must also characterize populations, because it is necessary to develop risk estimates for human populations of varied susceptibilities exposed to small concentrations of these pollutants.

The health problems that pollutants pose involve two major linked scientific issues. The first lies in the nature of the health problem itself. Is it an illness that is reversible, or self-limiting, or easily (or nearly universally) curable? Or is it an irreversible, self-perpetuating, hard-to-treat, often fatal illness, such as cancer? The second scientific issue lies in whether there is some level of exposure below which no health damaging effect will occur to any human. Such a dose level is called a "threshold." If a threshold for a material or a combination of materials can be shown, then a safe level can be easily set.

For many toxic reactions there is usually good biological reason to believe that a threshold will exist. If no clinical illness will occur unless some large number of cells is destroyed or damaged, then if a dose of a material damages or destroys far less than this number of cells, no clinical illness will follow, and we can safely say that the dose was below the threshold—and hence "safe." The problem of determining whether a threshold does exist is intimately related to the biology of the disease process. If the disease process can be initiated by a single event, following which the process is self-sustaining—requiring no further exposure—then the threshold will be at the level of the dose required to initiate that single event. If there are natural repair mechanisms that can reverse that single event or keep it from ever becoming self-perpetuating, and if this repair is complete up to some dose level where the mechanism is "overwhelmed," then there will be a threshold at the level just below the "overwhelming" level. Since it is very likely that the ability to repair varies from person to person, a repair-determined threshold in a population will be the threshold of the most sensitive persons in that population. If the same repair mechanism must deal with many materials, each of which contributes to its being overwhelmed, then it may be necessary to talk about threshold for added-on materials. An immediate consequence is that the possible threshold for these added-on or newer materials may already be fully consumed by other materials already present in the real world. If the repair mechanism is not complete, there will not be a threshold, and there will be some not as yet well understood modifications in the dose–response curves.

Given what is known today about the biology of cancer, mathematical models of dose response have been developed. No single model has captured all of the scientific community, and the different models currently being used and a more detailed consideration of threshold will be discussed later.

Because cancer is today believed to be a single event or multiple-event, self-perpetuating disease with a long latent period, and with (at present) little evidence of complete repair, it looks as if we must rely extensively on predictive techniques—mostly laboratory techniques—from the subcellular to the whole animal, whole life-time experimentation. Because of this need to rely on laboratory predictive techniques, it is useful to lay out current thinking about these techniques and to ask if it is reasonable or unreasonable to rely on them. These can be stated as a group of generally accepted 'principles."

General Principles

Principle 1

Effects in animals, properly qualified, are applicable to man. All of experimental biology and medicine makes this assumption. In cancer, this assumption seems thoroughly reasonable, because cancer in humans and animals is strikingly similar. Virtually every form of human cancer has an experimental counterpart, and every form of multicellular organism is subject to cancer, including insects, fish, and plants. Despite differences in susceptibility between different animal species, between different strains of the same species, and between individuals of the same strain, carcinogenic chemicals nonetheless affect most species. A considerable body of data exists showing that exposures carcinogenic to animals are likely to be carcinogenic to humans and vice versa.

The first reported instance of chemical carcinogenesis was cancer of the scrotum in chimney sweeps, observed by the British surgeon, Percival Pott, in 1775. It took 140 more years to show that a substance implicated in human cancer was carcinogenic in animals. In 1915 Japanese scientists found that extracts from coal tar cause cancer when applied to the skin of experimental animals. Since then, many pure carcinogenic chemicals, including many isolated from a wide variety of "tars" derived from incomplete combustion of organic matter, such as coal, wood, and tobacco, have been shown to produce cancer. There is little doubt that chemical products of burning, alone or in combination, are responsible for the greatly increased incidence of lung cancer among smokers. With the possible exception of arsenic and benzene, all known carcinogens in man are also carcinogenic in some species, although not in all that were tested.

Principle 2

Methods do not now exist to establish a threshold for long-delayed effects of toxic agents such as cancer. In classical toxicology, maximal tolerated (no-effect) doses in humans have been set on the basis of finding a no-observed-adverse-effect dose in acute experiments in animals and then dividing this dose by a "safety factor" of, say, 100, to designate a "safe" dose in humans. The obvious assumption is that a threshold lies below the no-observed-effect dose, and certainly above that dose divided by a safety factor. There is no scientific basis for similar estimation of a safe dose when one looks at chronic effects. In addition, the level of the no-effect-observed dose is strongly dependent upon the sample size of the experiment. For example, if no tumors are obtained in an assay of 100 animals, this implies that at a 95% confidence level the true incidence of cancer in this group of animals is less than 5%. If we used 1000 animals for assay at a single dose and no tumors appeared, we could only be 95% sure that the true incidence were less than 0.5%. For a disease such as cancer 0.5% is a very high risk for a large human population.

There are other problems in relation to animal experimentation. It is not clear what the operating characteristics are of most test systems. That is, we do not know how often the system will mislead by labelling a material as "positive" when it is not a carcinogen, or by labelling it "negative" when it really is a carcinogen.

There are no reasons to assume that false-negative results of carcinogenicity tests are more or less frequent than false-positive ones. Labeling as "carcinogen" a substance that gave rise to increased incidence of tumors requires the development of a biological rationale of a causal relationship. Similarly, to dismiss all compounds that did not induce tumors in one or two mouse and rat experiments as noncarcinogenic is sure to lead to errors.

Experimental procedures that use even large numbers of animals are likely to detect only strong carcinogens. When negative results are obtained in such bioassays, it is not certain that the agent tested is unequivocally safe, but our personal level of confidence is probably higher. Therefore, we must accept and use possibly fallible measures of estimating hazard to man. To make these measures less fallible leads to Principles 3 and 4.

Principle 3

The exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible carcinogenic hazards in man. The most commonly expressed objection to regulatory decisions based on carcinogenesis observed in animal experiments is that the high dosages to which animals are exposed have no relevance to human risks. In general, dosages that are high in relation to expected human exposures must be given because in model experimental systems, we have no choice but to use few animals in comparison with the number of humans exposed.

An incidence of cancer of about 10% in a group of experimental animals represents a lower limit of reproducibility; 10% of a human population is very high. For example, an incidence as low as 0.01% would represent 1000 people in a total population of 10 million and might be considered unacceptably high even in the face of sizable benefits. To detect such a low incidence in experimental animals directly would require hundreds of thousands of animals. For this reason, we have no choice but to give large doses to relatively small experimental groups and then use biologically reasonable models in extrapolating the results to estimate risk at low doses. Several models for making such calculations have been used. We think that the best method available to us today is to assume no threshold and a direct proportionality between the size of the dose and the incidence of tumors. This model is a conservative, public-health-oriented approach, but even it could underestimate risks. A human lifetime is some 35 times that of a mouse, and there is evidence that the risk of cancer increases rapidly with the length of exposure. Moreover, experimental assays are conducted under controlled dietary and environmental conditions with genetically homogeneous animals, whereas humans live under diverse conditions, are genetically heterogeneous, and are likely to include subpopulations of unusual susceptibility and unusual resistance.

Direct application of the linear, no-threshold model does not take into consideration species differences in susceptibility. For example, β-naphthylamine is well established as a human carcinogen on the basis of epidemiologic studies of occupationally exposed humans, whereas experiments have not shown it to be carcinogenic, for example, in the hamster, which is relatively resistant. If the hamster data were used to extrapolate to man, risk would be grossly understated. A conservative procedure would require that we use the most sensitive species to extrapolate to humans, recognizing that not all substances that cause a given incidence of cancer in the rat (or some other animal) are equally carcinogenic for man. This means that chronic-toxicity studies, which are imperfect assay systems for carcinogenicity testing,

should not be used as the sole criterion in the assessment of risk. How other data can be used, however, is not clear.

Principle 4

Material should be assessed in terms of human risk, rather than as "safe" or "unsafe." The current experimental techniques do not allow us to establish safe doses of materials shown to be carcinogens in animal testing, but with the help of statistical methods we may be able to estimate a reasonable upper limit of risk to human populations, if we have data to estimate population exposure, an appropriate and reproducible assay in animals, and satisfactory statistical methods. Some important limitations must be recognized. First, no single generally applicable procedure can be recommended for testing all toxic agents. The well-informed expert investigators will have to design appropriate assays recognizing that they will always be subject to the scrutiny of their peers. If substances that affect large populations are found to be carcinogenic, broad scope experiments may have to be conducted, to obtain more detailed information on their possible effects in humans. As a pragmatic guideline, it has been suggested that a potential carcinogen be tested in at least two species, such as the mouse and the rat, in strains of animals that have a low incidence of spontaneous tumors under the conditions of the test. It may be necessary to include "positive" controls, with known carcinogens, under the same conditions used for the test animals.

Experiments should be conducted over as much as possible of the lifetime of the experimental animal. The highest dose should be the maximum that is tolerated without shortening the lifespan through causes other than cancer. Every animal, whether it dies during the exposure period or is sacrificed at the end of the experiment, should be examined grossly and microscopically, and all toxic effects (not only cancer) should be noted.

Models for Extrapolation

Several mathematical models for extrapolation have been proposed. To be meaningful, they must relate to biological theories of carcinogenesis. There is no dearth of quantitative theories of carcinogenesis that relate the frequency of detectable tumors to the intensity of exposure to the carcinogen. The purposes of these theories are twofold: to elucidate the mode of action of the carcinogen and the nature of the neoplastic change and to estimate, from animal experimentation, the risk to human populations exposed to environmental concentrations of the carcinogen.

One of the earliest quantitative theories was that of Iverson and Arley (*1, 2*). Their model was basically a one-step transition process occurring in a single cell. A cell starts out being "normal" and has some positive probability of being transformed to a cancer cell. Iverson and Arley assumed that this transition probability was a linear function of the amount of the carcinogen, the intercept of this linear function representing the background or spontaneous transition probability, as would obtain if none of the carcinogen were present. After transition to a cancer cell, Iverson and Arley assumed, the growth of the clone could be represented by a pure birth process with a birth rate independent of the initial amount of the carcinogen. The clone was assumed to become a detectable tumor when it reached a given size. This model is commonly referred to as the one-hit model and implies that the expected number of tumors within a lifetime will depend only on the total dose and not on the pattern of exposure. The mathematical forms of a wide class of hit-theory models were given by Turner (*3*) who developed the mathematical theory between the "hits" of an agent and the critical targets. He also discussed extensions that include both biologic variation in the probability of a hit and variation in the number of critical targets.

Nordling (*4*) and Stocks (*5*) each carried the Iverson-Arley model forward in proposing models in which a single cell can generate a tumor only after it has undergone more than one change or mutation; these could be termed multievent theories of carcinogenesis. They assumed that the probabilities of transition from one state to the next within some time frame were the same and were proportional to both time and the concentration of the carcinogen. Like Iverson and Arley, Nordling and Stocks assumed that the growth time of the tumor after the last event had occurred was either independent of the carcinogen or showed a negligible dependence on dose. When the number of necessary changes is about 6 or 7, this model yields age-specific cancer incidence rates that are proportional to the fifth or sixth power of age and in this respect the model is consistent with human incidence data. However, the model also predicts that cancer incidence is proportional to the same high powers of the concentration of the carcinogen; this is not in agreement with the results of human and animal data. To avoid this discrepancy, Armitage and Doll (*6, 7*) modified the theory of Nordling and Stocks by assuming that the probabilities of transition between events were not all equal. They also assumed that only some of the transitional events depended on the carcinogen and that the remainder had a proba-

bility of spontaneous transition independent of the level of the carcinogen in question. With this modification, the model became consistent with both human and animal data that showed tumor incidence as related to either dose or the square of dose, but not higher powers.

In the dichotomous-response situation, the multievent theory of carcinogenesis proposed by Armitage and Doll (*7*) leads to a mathematical model that relates the probability of response $P(d)$ at the dose d by

$$P(d) = 1 - \exp\{-(\lambda_0 + \lambda_1 d + \lambda_2 d^2 + \ldots + \lambda_k d^k)\}$$

where k represents the number of transitional events in the carcinogenic process that are related to the carcinogen under test and $\lambda_o, \lambda_1, \lambda_2, \ldots, \lambda_k$ are unknown nonnegative parameters. As with the other "linear-at-low-dose" models, for small enough values of the exposure d, this dose-induced response rate will be approximately equal to $\lambda_1 d$ (assuming that λ_o is the "background" rate.) Therefore, in extrapolating from high dose levels to low doses, the risk attributable to the carcinogen, after correcting for background, will depend on the magnitude of the linear coefficient λ_1.

In practice, when this model is applied to the problem of risk estimation, the model is to be fit to the experimental data by some such procedure as maximum likelihood. A point estimate of the attributable risk may be obtained from the model with the estimated parameter, but, to incorporate the vagaries of random sampling, it would be prudent to include the upper statistical confidence limit on this risk estimate.

It should be noted that the theories of Nordling, Stocks, and Armitage and Doll are based on the concept that carcinogenesis has a single-cell origin, whereas a theory proposed by Fisher and Holloman (*8*) is multicellular in concept. They proposed that a tissue of N cells must contain at least K cells that have undergone some transformation, for a tumor to occur in the tissue. This theoretical approach leads to a model very similar in form to the multievent model. Other multievent theories have been proposed that incorporate the concepts of cell death or loss of ability to divide (*9*) and modifications that permit cells in intermediate stages to grow more rapidly than normal (*10*). In part, the approach by Burch also includes such concepts as repair—the death of a precancer cell being equivalent to the repair of that cell, in the sense that having died or having been repaired the cell will not go on to develop as a cancer.

Crump et al. (*11*) discussed many of these models of carcinogenesis from the viewpoint of low-dose kinetics. They made two basic assumptions: that the cancer process is single-cell in origin possibly with multiple steps between initiation and complete alteration, and that the growth period of the completely altered cell is basically independent of the initiating dose. For direct carcinogenic processes, in which the agent or its metabolite acts at the cellular level to produce an irreversible change, they concluded that most models of carcinogenesis will be linear for low doses. In addition, they showed that, if it can be assumed that the environment contains carcinogens that act in conjunction with the tested agent, then all the models thus far proposed will be linear for low doses.

Dose Considerations

In all these theories, the emphasis is mainly on the stochastic nature of the changes involved in the carcinogenesis process. The role played by the carcinogen is considered to a much lesser degree. It is commonly assumed that the transitional events in the process attributable to the carcinogen occur with probabilities proportional to the exposure. This is undoubtedly an oversimplification of the actual process. The actual exposure is modified by absorption, distribution, metabolism, and excretion of the chemical substance, and the effective exposure should probably be the actual concentration of the carcinogen at and within the target cells. Other factors that may affect delivery of the carcinogen to intracellular compartments are membrane permeability and enzyme binding. Therefore, the "effective dose" may well be some complex function of the actual exposure and the biochemical and physiologic characteristics of the host. Most of these mathematical models incorporate the dose as it is actually administered in animal experiments or human exposure. The function relating administered dose to "effective dose," if it is not a simple case of proportionality, can have a profound effect on the dose-response relationship. As a simple example, consider a linear model relating dose (effective dose) to response. If the effective dose is proportional to the administered dose, then a linear model obtains for administered dose versus response. If the dose relationship is concave, which would obtain if the incremental increase in effective dose decreases with higher doses, then the relationship between administered dose and response would also be concave. Thus, the various dose-response curves that have been observed may not be indicative of different carcinogenic processes once the agent has reached the target cell, but rather may indicate different functions relating to how an administered dose becomes an effective dose. This

problem will probably relate more to chemical carcinogenesis, as opposed to radiation induced cancer.

Repair, Destruction, and Threshold

Even if a normal cell has been transformed to some intermediate stage in the carcinogenic process, this would not necessarily mean that cancer must occur. Cell repair or recovery or some other response from the immume mechanisms (i.e., cell destruction) may be sufficient to stop or reverse the process before the self-perpetuating stage is reached. In addition, the death of these transformed cells may occur before the process has a chance to continue toward the eventual cancer. This is one of the major arguments in favor of the existence of a threshold. However, if there is some probability that these recovery or destruction mechanisms will not complete their role before the occurrence of another event or transformation, then this type of threshold will not exist.

Thresholds may be considered from two viewpoints: an "actual" threshold, which is an exposure below which any carcinogenic response attributable to the specific agent is impossible; and a "practical" threshold, which is an exposure below which an attributable carcinogenic response is highly unlikely. In discussing carcinogenic thresholds, Mantel (*12*) has argued that whether "actual" thresholds exist is of less importance than "practical" thresholds when estimating human risk. He has suggested procedures for extrapolating the results of animal experiments performed at necessarily high exposures to the lower exposures of humans. He and Bryan (*13*) stated that a risk of cancer of 1 in 10^8 could be thought of as a "virtually safe" level and that efforts should be made to estimate exposures that would produce no more than this risk. Using mathematical models that relate the latency period (time between initiation of exposure and appearance of cancer) to the exposure, Jones (*14*) suggested that a "practical" threshold could be defined as an exposure for which the latency period is beyond the normal lifespan.

Experimental or observational evidence of the existence of a threshold is usually presented in the form of a dose–response graph in which the percentage of animals with tumors or the average number of tumors per animal is plotted against the dose of the carcinogen. Either the existence of doses not leading to an increase in tumor incidence over controls or the extrapolation of such curves to low doses that apparently would result in no tumor increase is cited as an indication of the existence of a threshold below which no response is possible. This type of evidence is an exercise in self-deception.

First, as noted earlier, the observation of no positive responses does not guarantee that the probability of response is actually zero. From a statistical viewpoint, zero responders out of a population of size N is consistent at the 5% significance level with an actual response probability between zero and approximately $3/N$ (e.g., when N = 100 and zero responders are observed, the true probability of response may be as high as 3%).

Second, when an observed plot of dose against tumors is extrapolated downward to produce a no-effect dose, it is assumed that the observed dose-response relationship, usually linear, will obtain throughout the entire spectrum of doses and that one threshold exists for the entire population at risk. The assumption of linearity throughout the entire dose spectrum can easily lead to erroneous conclusions. For example, consider the true dose-response relationship shown by the dashed curve in Figure 1. This curve is convex, which would be consistent with a multievent theory of carcinogenesis in which more than one event is affected by the carcinogenic agent. This type of convex dose–response relationship, when sampled in an animal experiment over only a part of the dose range, could be thought to imply the existence of a threshold if simple linear extrapolation is used. If the animal experiment is performed at doses between A and B, one could conclude that a threshold exists at dose d_i, if the experiment is performed at

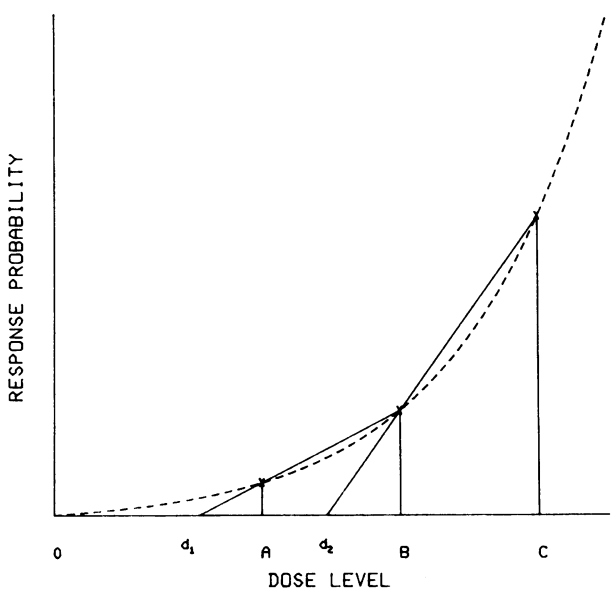

FIGURE 1. Linear extrapolations obtained from convex dose-response curve.

doses between B and C, the conclusion could be a higher threshold at dose d_2. In fact, for convex dose–response curves, if the experiment is performed over any range of doses that appears to produce linearity between dose and response, then simple linear extrapolation will always imply the existence of a threshold.

In addition, the assumption of one threshold is unrealistic. It is much more likely that, if thresholds do exist, not all members of the population have the same one. The human population is diverse and genetically heterogeneous, and is exposed in different degrees to a large variety of toxic agents. Many different disorders may affect the frequency of mutational events in specific tissues. Disorders characterized by chromosomal instability have been found to be predisposed to malignancy. Patients with xeroderma pigmentosum are highly susceptible to ultraviolet-induced skin cancer, and it has been found that they have deficient DNA repair mechanisms (*15*). In Bloom's syndrome, there is an immune deficiency and an increased risk of leukemia and cancer of the colon (*16*). Although there have been problems in reproducing the early results, there is some evidence that the amount of an enzyme, aryl hydrocarbon hydroxylase (AHH), which is genetically controlled, may determine the susceptibility to lung cancer from cigarette smoking (*17*). This system may provide a model in which the risk of mutation and subsequent malignancy after exposure to an environmental carcinogen may be genetically determined. If malignancy is the result of a series of mutational events, then there must be subpopulations at various degrees of risks or with various thresholds for the carcinogenic agent. Therefore, the search for thresholds should not be a search for one specific no-effect dose applicable to all members of the population at risk: rather, the problem is to find many thresholds for each of the subgroups in the population.

This variability in thresholds or susceptibility to carcinogenic agents has been shown by Mantel (*18*) to induce an increased convexity in dose-response curves at low doses. They demonstrated that a linear dose–response curve with a fixed threshold will become convex at low exposures, if the individual thresholds are allowed to vary. Therefore, the extrapolation of observed dose-response curves, when the individual thresholds actually vary in the population, will, at best, lead simply to the average threshold of the population at risk. An estimate of the average threshold will have little practical utility, because many members of the population will have individual thresholds below this value. In addition, if we are willing to assume that threshold variability is the likely state in nature, then from a statistical viewpoint it is practically impossible to distinguish between mathematical models that hypothesize different thresholds and multievent models that hypothesize no thresholds, because the shapes of the two models can be very similar, and in some cases identical. For example, a one-hit dose-response model with a threshold may be written as,

$$P(d/\lambda) = \begin{cases} 0 & d < \lambda \\ 1 - \exp\{-\alpha(d - \lambda)\} & d \geq \lambda \end{cases}$$

where $P(d/\lambda)$ represents the dose-induced response rate at a dose level d and λ is the threshold below which no response can occur. If we assume that the population consists of individuals with different thresholds and that these thresholds vary according to some probability distribution $F(\lambda)$, then the variable-threshold model is simply the convolution of $P(d/\lambda)$ with $F(\lambda)$,

$$P(d) = \int P(d/\lambda)dF(\lambda)$$

If, for computational simplicity, we choose $F(\lambda)$ to be an exponential probability distribution, then this variable-threshold model takes the mathematical form,

$$P(d) = 1 - \left[\frac{\exp\{-\alpha d\} - (\alpha/\beta)\exp\{-\beta d\}}{1 - (\alpha/\beta)}\right]$$

The interesting aspect of this particular mathematical model is that, as the ratio α/β approaches unity, the model becomes

$$P(d) = 1 - (1 - \alpha d)e^{-\alpha d}$$

which is the mathematical form of a two-hit model for dose response.

Discrimination among these models on the basis of animal experiments is often impossible. These three models were fitted to data from an experiment by Terracini et al. (*19*) in which dietary concentration of dimethylnitrosamine (DMN) of 0–20 ppm were fed to female rats. The experiment was continued for 120 weeks, and the appearance of liver tumors was the response variable. The data are shown in Table 1.

Table 1. Response to dimethylnitrosamine (DMN).

DMN in diet, ppm	Number responders / number at risk	Response rate, %
0	0/20	0.0
2	0/18	0.0
5	4/62	6.5
10	2/5	40
20	15/23	65

The fixed-threshold and variable-threshold models, in addition to the two-hit model, all fit these data equally well. There is no statistical basis on which to prefer one over the others. Experimental results like these, although appearing to give evidence of a threshold, will provide no statistical evidence either in favor of or opposed to the existence of such thresholds. Therefore, statistical analysis of standard animal carcinogenicity experiments is not now, and probably will never be, in a position to resolve the threshold question. There are too many "biologically reasonable" mathematical models, both implying and denying the existence of thresholds, that will fit the observed results.

The quantitative theories of carcinogenesis that have been proposed are all stochastic. They consider the probabilistic chances of the occurrence of some series of events. If one is willing to assume that these events have transition probabilities that can be affected by the carcinogen (no matter how small the concentration), that the systems of distribution and metabolism have some chance of allowing some amount of the carcinogenic agent to reach the target cells (no matter how small the chance or the amount), and that the repair, destruction and recovery systems may not do a perfect job (no matter how small the chance that this will happen), then there will be no exposure that will have a zero probability of leading to a cancer.

In addition, when considering the possibility of carcinogenic thresholds, one should keep in mind that no agent has been found to induce a type of cancer that had not been previously described. It is possible, perhaps even likely, that many carcinogenic agents act by the same mechanism on the same target cells. This would imply that, inasmuch as there are many carcinogenic agents in our everyday environment, some additional carcinogen could act in a simple additive manner and thus that any exposure would simply be added to the background. This means that, for a population already being exposed to carcinogenic agents, any additional carcinogen would simply increase the expected tumor incidence in a continuous manner, no matter how low the exposure to the additional agent. Therefore, despite all the complexities of the mechanisms of chemical carcinogenesis, because of genetic variation among members of the population at risk and because statistical analysis cannot resolve the question one way or the other, the search for an "actual" carcinogenic threshold is probably fruitless, and any human exposure to a carcinogen should be considered to be associated with some risk, no matter how small that risk may be. The current mathematical models that relate exposure to attributable risk are, at best, extremely crude tools. Much work needs to be done in refining these theories (*20*).

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